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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,099	LESLEY ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,22-27,33-37,40,41,43-57 and 61-74* is/are pending in the application.

4a) Of the above claim(s) *34-37,40,41, 43-57 and 61-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-13,22-27 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This Office Action is a reply to the Paper filed 31 August 2005 in response to the Non-Final Office Action mailed 1 June 2005. Claims 34-41, 43-59 and 61-74 have been withdrawn from consideration and claims 1-9, 11-13, 22-28 and 33 were considered in the 1 June Office Action. Claims 28, 38, 39, 58 and 59 were canceled and claims 1, 11, 46, 56, 57, 63, 64 and 73 were amended in the 31 August Paper. Claims 1-9, 11-13, 22-27, 33-37, 40, 41, 43-57 and 61-74 are pending and claims 1-9, 11-13, 22-27 and 33 are under consideration.

Claim Objections

Claims 1, 38, 39, 40, 67 and 71 are objected to because of the following informalities:

Claim 1 includes the markings showing changes made in the previous claim set (*i.e.*, the word "recombinant" is underlined in part (a) and the word "prokaryotic" is lined through), claims 38 and 39 are canceled but the claim text is present and the status identifiers for 40, 67 and 71 are not among those approved under the new Rule 1.121(c) or the accepted alternatives set forth in the 6 June 2005 pre-OG notice available at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/noncompliantOG-060105.pdf.

Although the amendment is technically not compliant with the requirements of Rule 1.121, because the scope of claim 1 and the status of claims 38, 39, 40, 67 and 71 is not rendered unclear by the informalities, and in the interest of compact prosecution, the claims have been examined. Applicant is urged to review the requirements of 37 CFR §1.121 and adhere to those requirements in future submissions.

Appropriate correction is required.

Response to Amendment and Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection of claim 28 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112, first paragraph

Claims 1, 2, 4-6, 8, 9, 11-13, 22-27 and 33 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record and herein below.

The *prima facie* case set forth in the Office Action mailed 18 June 2003 contends that the skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of solubility responsive promoters encompassed by the host cell of the claims.

Response to arguments

In response to the *prima facie* case and arguments of record, Applicant has amended the claims such that the host cell is limited to an *E. coli* host cell, which amendment overcomes the grounds for rejection set forth in the previous Office Action at pages 6-7. With regard to the scope of the solubility reporter genes comprised within the host cell, Applicant contends that the

claims to a host cell comprising a solubility reporter nucleic acid construct comprising a protein solubility responsive promoter is distinct from claims directed to a solubility responsive promoter *per se*. On page 14, Applicant contends:

> For a hypothetical claim that is directed to a genus of protein solubility responsive promoter per se, the structural information of the promoter would be an essential element. For such a claims it might be reasonable to require that the structural information of the disclosed species be representative of the entire genus. However, it must be emphasized that the presently rejected claims are not directed to a genus of protein solubility responsive promoters. Rather, the presently claimed invention (e.g.. claim 1) is directed to host cells which harbor a protein promoter solubility responsive promoter for examining solubility of a target protein, and to methods employing such host cells. Unlike the hypothetical claim, the employed promoter is not an essential element of the claimed invention on which patentability is predicated. So long as the promoter is responsive to expression of an insoluble protein in the host cell the exact nature or identity (e.g.. structural information) of the employed promoter is inconsequential to the practice of the claimed invention.

While acknowledging that claims directed to a genus of protein solubility responsive promoters per se might need to include structural information that is representative of the entire genus, Applicant asserts that the same should not be applied to claims directed to methods or compositions that merely employ a protein responsive promoter to assess solubility of a target polypeptide. Applicant contends that it is the ability of the disclosed promoters to be responsive to expression of insoluble proteins that need to be representative of the entire genus.

These arguments have been fully considered but are not deemed persuasive. As stated in the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, first paragraph, 'Written Description' Requirement" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices), "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An

applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

Applicant's position is that the solubility responsive promoter is not a critical element of the claimed invention because, so long as the promoter is responsive to insoluble protein, the exact nature or identity of the employed promoter is not important (page 14, lines 20-25). However, the solubility responsive promoter is clearly a critical element of the claimed host cell because the functional properties of the host cell are defined by the solubility responsive promoter. Applicant's contention that "compositions that merely employ a protein solubility responsive promoter to assess solubility of a target polypeptide" is not persuasive because, clearly, the solubility responsive promoter itself is critical to assessing solubility of the target polypeptide (*i.e.*, the functional property that defines the claimed invention).

While it is acknowledged that the promoter need only be responsive to insoluble protein, for the reasons set forth in previous Office Actions, the disclosure fails to set forth the relevant, identifying characteristics that define a genus of promoters responsive to insoluble protein such that the skilled artisan would recognize that Applicant was in possession of the host cell now claimed. Specifically, although Applicant has disclosed a variety of promoters that have been empirically determined to exhibit altered expression in the presence of insoluble protein, there is no disclosure of the structural elements that define the functional properties of a solubility responsive promoter such that the skilled artisan would recognize that Applicant is in possession of the genus of host cells now claimed.

Applicant cites MPEP § 2163-II-A-3-(a)-ii) and the case of *In re Rasmussen* (650 F.2d 1212, 1214, 211 USPQ 323, 326-27 (CCPA 1981)), wherein the court held that "disclosure of a

single method of adheringly applying one layer to another was sufficient to support a generic claim to 'adheringly applying' because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered." Applicant contends that according to the logic of *In re Rasmussen* the exact sequence of the protein solubility responsive promoters is not important so long as they can respond to expression of insoluble proteins.

This argument is not found persuasive. MPEP §2163 II A 2. makes the following distinction (emphasis in *Amgen* added):

> An element may be critical where those of skill in the art would require it to determine that applicant was in possession of the invention. Compare *Rasmussen*, 650 F.2d at 1215, 211 USPQ at 327 ("one skilled in the art who read Rasmussen's specification would understand that it is unimportant how the layers are adhered, so long as they are adhered") (emphasis in original), with *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) ("it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it").

The invention in the instant case is clearly more analogous to the chemical compound at issue in *Amgen* (*i.e.*, the element at issue in the written description rejection is a chemical compound having the activity of a solubility responsive promoter, which element is critical to the functional properties of the claimed cell as a whole) than to the method of manufacturing a thermal insulating member comprising adheringly applying one side of a tubular plastic film at issue in *Rasmussen*. The court in *Rasmussen* states, "An applicant is entitled to claims as broad as the prior art and his disclosure will allow" (page 326). The Court in *Amgen* states, "We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved

until reduction to practice has occurred, *i.e.,* until after the gene has been isolated." For reasons of record, the application fails to disclose the solubility responsive promoter, a critical element of the claimed host cell, such that the skilled artisan would be able to envision the detailed constitution thereof so as to distinguish it from other materials.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Thus, for reasons of record and herein, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Claim Rejections - 35 USC § 112, second paragraph

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim was found indefinite in reciting "a mutated form of a polypeptide" because there is no explicit definition of what constitutes a "mutated form" of a polypeptide and the claim fails to set forth a benchmark with which to determine whether a polypeptide is "a mutated form". Because all polypeptides might be considered "mutated" relative to some other polypeptide (*i.e.*, a polypeptide having any one or more differences in amino acid sequence relative to another polypeptide) and all polypeptides have evolved to their present form by a process of mutation, it is not possible to ascertain whether a polypeptide meets the limitation unless it is clear what defines a polypeptide that is not mutated.

Response to arguments

In response to the *prima facie* case of record, Applicant contends that to a skilled person in the art of biochemistry and molecular biology the meaning of a mutated polypeptide should be apparent in any given context. Applicant urges that one would understand that a mutated polypeptide is relative to the wildtype form of the molecule that naturally exists in a wildtype host that harbors the molecule, that the mere existence of many possible mutated forms of a polypeptide does not render the recited term indefinite, that Applicants should not be required to provide definition of a term that is well understood in the relevant arts and that it is not reasonable or possible for Applicants to set forth all possible mutant forms of a polypeptide.

These arguments have been fully considered but are not deemed persuasive. Applicant contends that the skilled artisan would understand that a mutated polypeptide is relative to the naturally occurring wild type form of the molecule, but there is nothing in the specification that would require that the naturally occurring wild type form is the benchmark for determining whether a polypeptide is mutated. In contrast, the term "mutated" is commonly used in the biochemical arts to refer to any polypeptide comprising a sequence modification relative to another polypeptide sequence. For example, a biochemist might consider any polypeptide sequence that is the product of a process of *in vitro* mutagenesis as mutated, relative to the starting material, regardless of the relationship of the polypeptide sequence to the "wild type" form of the polypeptide. The claim, as written, essentially limits the target polypeptide to being different without specifying from what the polypeptide differs.

Furthermore, Applicant's position that a mutated polypeptide is relative to the wildtype form of the molecule that naturally exists in a wildtype host is itself ambiguous because it is well known that many polypeptides comprise polymorphisms, which do not result in a mutant

phenotype. Even if one were to assume, *arguendo*, that the skilled artisan might interpret a claim narrowly as limited only to proteins that comprise mutations relative to "wildtype", it is unclear how "wildtype" is to be defined. Is the "wildtype" form of a polypeptide to be construed as the predominant form or does it more broadly encompass any naturally occurring polypeptide?

Because the limitation "mutated form" is subject to a variety of interpretations and the disclosure fails to clearly indicate how the term is to be construed, the skilled artisan is unable to ascertain what is covered by the claim. Therefore, the scope of the claimed subject matter is indefinite.

Double Patenting

Claims 1-9, 11-13, 22-27 and 33 **stand provisionally rejected** under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 4-14 of copending Application No. 10/127,078 and over claims 1-18 and 22-33 of copending Application No. 09/991,499 for reasons of record. Applicant's willingness to address the provisional rejections once claims in the copending applications have been issued is acknowledged. Until such time as the rejection is addressed the claims will stand rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 8, 11, 13, 22-27 and 33 **stand rejected** under 35 U.S.C. 102(b) as being anticipated by Farr U.S. Patent No. 5,589,337 (made of record in the IDS filed 7 November 2002).

Response to Arguments

In response to the *prima facie* case set forth in the 1 June Office Action, Applicant has amended the claims to recite that the host cell comprises "a recombinant solubility reporter nucleic acid construct" and "a second nucleic acid construct that comprises a polynucleotide that encodes a target polypeptide". Applicant contends that the claims are now free of the art because Farr *et al.* teaches that the lacZ gene and ampicillin resistance gene, which were construed as encoding target polypeptides, are part of the same cloning vector into which the stress promoter is cloned. Applicant construes the amended claims as requiring that the target polypeptide-expressing nucleic acid is located in a separate nucleic acid construct that is independent of the construct that harbors the solubility promoter and the reporter gene. In the first full paragraph on page 17, Applicant states, "Applicants have herein amended the claims to more clearly specify that the solubility promoter/reporter gene and the polynucleotide expressing the target polypeptide are present on two separate nucleic acid constructs".

These arguments have been fully considered but are not deemed persuasive because they are based on an overly narrow reading of the claims. Paragraph 0030 of the specification defines the expression constructs of the invention as "a polynucleotide comprising a promoter element operatively linked to a gene". There is nothing in the specification to suggest that the limitation

"construct" or "polynucleotide construct" requires that the recombinant solubility reporter nucleic acid construct and the nucleic acid construct that comprises a polynucleotide that encodes a target polypeptide heterologous to the host cell be comprised on separate vector molecules, as implied by applicant's arguments. Instead, a first and second polynucleotide construct is reasonably construed as encompassing, at least, any combination of a first and second polynucleotide expression construct, regardless of whether those expression constructs are on the same or different vector molecules.

As described in the previous Office Action, Farr *et al.* teaches *E. coli* host cells are transformed with reporter constructs comprising an ampicillin resistance gene and a lacZ gene (see especially the first paragraph in column 20). As the host cell does not comprise an endogenous ampicillin resistance gene or lacZ gene and either of the polypeptides would cause a change in expression of the reporter gene when expressed in insoluble form were the reporter gene operably linked to a solubility responsive promoter as contemplated by Farr *et al.*, the ampicillin resistance gene and lacZ gene of Farr *et al.* meet the limitations of the target polypeptide-expressing nucleic acid of the instant claims. Furthermore, because at least the ampicillin resistance gene target polypeptide encoding construct and the solubility reporter polynucleotide construct of Farr *et al.* can reasonably be construed as distinct polynucleotide constructs (*Id.*), the host cell of Farr *et al.* anticipates the host cell of the instant claims as amended.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §102 as anticipated by Farr *et al.*

Claim Rejections - 35 USC § 103

Claims 1-8, 11, 13, 22-27 and 33 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Farr *et al.*, as applied to claims 1, 5, 8, 11, 13, 22-27 and 33 above, and further in view of Allen et al. (1992) *J. Bacteriol.* 174:6938-6947 for reasons of record and herein below.

Response to Arguments

As described above, in response to the *prima facie* case set forth in the 1 June Office Action, Applicant has amended the claims to recite that the host cell comprises "a recombinant solubility reporter nucleic acid construct" and "a second nucleic acid construct that comprises a polynucleotide that encodes a target polypeptide". Applicant contends that the claims are now free of the art because Farr *et al.* teaches that the lacZ gene and ampicillin resistance gene, which were construed as encoding target polypeptides, are part of the same cloning vector into which the stress promoter is cloned and Allen *et al.* does not cure this deficiency. This argument is not deemed persuasive because, for the reasons set forth herein above, Applicant's argument is based on an erroneous construction of the claims and Farr *et al.*, in fact, anticipates the base claim in view of the broadest reasonable interpretation thereof.

Applicant further contends that there would not have been suggestion or motivation to combine teachings of the cited references and that of any other art that might render the subject matter obvious because Farr *et al.* expressly teaches away from the presently claimed invention. In support of this, Applicant points to a teaching indicating that it is preferable that the host strain

be homologous with the stress promoter and that "the strain should be wild type for all other genes *especially stress genes*" (emphasis added by Applicant).

This argument has been fully considered but is not deemed persuasive. First, it is unclear exactly which limitation in the claims Applicant believes Farr *et al.* is teaching away from in this statement. Nevertheless, as discussed above, Farr *et al.* anticipates the limitations of the base claim. Allen *et al.* is relied upon for a teaching of the promoter region from the E. coli ibpA gene and that the ibpA gene is responsive to the presence of a high level of unfolded proteins. The passage cited by Applicant, viewed in context, merely teaches that it is preferable that the host cell strain be homologous with the stress promoter used and that the host cell genome comprise all of the endogenous stress genes. As the ibpA promoter of Allen *et al.* is an *E. coli* promoter and the host cell of Farr *et al.* is *E. coli*, the skilled artisan would not have viewed the teachings of Farr *et al.* as a teaching away from using a promoter such as the ibpA promoter of Allen *et al.*

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §103(a) as obvious over the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of objection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER